Appendix C

Review

Calcium, Vitamin D, and Colorectal Cancer: A Review of the Epidemiologic Evidence

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Abstract

A protective effect of calcium on colorectal cancer, one of the most common malignancies in Western societies, has been supported primarily by results of *in vitro* animal studies. The present review summarizes the available epidemiological evidence for the association between calcium, vitamin D, and colorectal cancer. The overall results from over 20 published case-control and cohort studies suggest that calcium intake is not associated with a substantially lower risk of colorectal cancer. Findings from large prospective cohort studies, which should be least affected by methodological bias, have been notably consistent in finding weak and nonsignificant inverse associations. Whereas the relation between calcium and colon or colorectal cancer has been studied in numerous epidemiological studies, the role of vitamin D has only been addressed in a few of these investigations. The available results for vitamin D suggest that this micronutrient is inversely associated with risk but, given the scarcity of data, additional studies are needed to investigate this relation in more detail.

Introduction

Although a genetic predisposition may be important in some individuals, diet is thought to be a major etiological factor for colorectal cancer (1–5). A possible protective effect of calcium against colon carcinogenesis has been suggested by results of animal studies (6–9) and *in vitro* studies in human epithelial cells (10). It is hypothesized (8, 11) that calcium might reduce colon cancer risk by binding secondary bile acids and ionized fatty acids to form insoluble soaps in the lumen of the colon, thus reducing the proliferative stimulus of these compounds on colon mucosa. It has also been suggested (12) that calcium can directly affect the proliferative activity of the colon mucosa. Intervention studies in humans on the effect of calcium supplementation on cell proliferation have yielded inconsistent findings (10, 12, 13–20). Vitamin D may protect against colorectal neoplasia by reducing epithelial cell proliferation and inducing differentiation, and this activity may be mediated through the vitamin D receptor (21–22). Experimental findings in humans and animals suggest that vitamin D inhibits cell proliferation (21–24).

Despite the considerable number of studies in humans, in cultured colonic malignant cell lines, and in experimental animal models, the possible roles of calcium and vitamin D as colorectal anticarcinogens remain unclear.

Ecological Studies

Rates of colorectal cancer vary widely around the world. Variation in rates is also observed within countries when different regions or religious groups are compared. The relation between colorectal cancer and calcium intake can be assessed by examining associations between cancer rates as they occur in different populations and their corresponding dietary habits. A number of investigators have reported associations between *per capita* consumption of milk or milk products and national colon or colorectal cancer incidence or mortality rates (25–33). Overall, these correlational data do not support the notion that intake of milk or milk products is inversely associated with risk of colorectal cancer. When data for milk or milk product consumption is plotted against rates of colon cancer mortality, a suggestion of a positive association emerges (Fig. 1). One apparent exception in these data is Finland, where the *per capita* consumption of milk and milk products is high, yet the rate of colon cancer mortality is relatively low. Sorenson *et al.* (34) have noted that areas in rural Finland, where consumption of calcium is high, have one of the lowest colon cancer incidence rates among the developed countries, whereas Helsinki, Finland has a higher incidence rate and a lower level of calcium intake. Furthermore, Reddy *et al.* (30) reported a greater intake of milk in Finland, a country with low rates of colorectal cancer, than in New York, a region of high rates but with comparable fat consumption to that of Finland. McKeown-Eyssen and Bright-See (35) have conducted a more complex analysis of their ecological data. In their results, the correlation between the availability of milk and milk products and age-adjusted colon cancer mortality was 0.40; after adjustment for the availability of animal fat, the correlation changed to −0.30.

Variations in colon cancer rates are also seen within countries. In the United States, Mormons, who consume greater quantities of milk products, have lower rates of colorectal cancer than all United States white individuals (31). However, they have other dietary practices different from the rest of the United States. Similar observations have also been made in Japan (29), where a negative association was seen between milk product consumption and colorectal cancer rates; however, no account was taken of potentially confounding factors.

Traditionally, ecological studies have been considered the weakest form of epidemiological evidence. The primary problem of these correlational studies is that many potential determinants of colorectal cancer other than the dietary factor under consideration may vary between areas with high and low incidence rates. Such confounding factors can include genetic pre-

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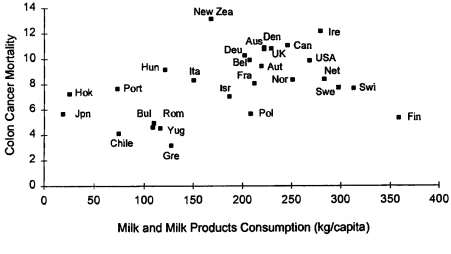

Fig. 1. Standard mortality rates for 1971 per 100,000 population, ages 0–64 years, for cancer of the colon, rectum, rectosigmoid junction, and anus. WHO. Food and Health Indicators in Europe [software issued by the WHO Regional Office for Europe (Copenhagen, Denmark) September 1993]. Milk and milk products consumption from 1961.

disposition, other dietary factors, and other environmental or lifestyle practices. Although the dietary information can be improved and the analyses can be refined, the results will not be independent of potentially confounding variables. Another serious limitation of the international correlational studies is that they cannot be independently reproduced, which is an important part of the scientific process. Thus, ecological studies have been useful, but they are not sufficient to provide conclusions regarding the relationships between milk or calcium consumption and colon cancer.

Analytic Epidemiological Studies. Calcium. Analytic epidemiological studies that have examined the association between calcium as a risk factor for colorectal cancer have been inconsistent. There is some evidence in support of a weak inverse association between relatively high intakes of calcium and risk of colorectal cancer (Table 1). Fifteen case-control studies (36–50) and eight cohort studies (51–58) have reported results for the association between calcium and colorectal, colon, or rectal cancer. Inverse associations were reported in most of these studies (36, 37, 39–41, 44, 46–49, 51–58), but this was significant in only five of the case-control studies (37, 39, 44, 46, 49) and in one of the cohort studies (51). A positive, nonsignificant association was reported in five studies (38, 42, 43, 45, 50). Of interest, data from the large cohort studies are quite consistent in showing weak, nonsignificant inverse associations. However, the dose-response relationships from these data are less impressive. In the large cohort studies in which a comprehensive assessment of usual diet was used, the inverse associations seem to result from a slight increase in risk in the lowest category of calcium intake rather than a reduction in the highest group (Fig. 2). It is also important to note that dietary data for three of the reported prospective studies in the United States (55, 57–58) were based on a food frequency questionnaire that has been shown to be reasonably valid in comparison with detailed weighted diet records (59–60). Furthermore, in both the Health Professionals Follow-Up Study (61) and the Nurses' Health Study (62), the same measure of calcium intake clearly predicted risk of kidney stones.

Results of a recent meta-analysis report of analytical epidemiological did not support a substantial protective effect of calcium on colorectal carcinoma (63); the RR[2] for the association between calcium and colorectal cancer, based on data from 24 studies, was 0.86 (95% CI, 0.74–0.98). The authors conducted analyses in subgroups defined by gender, tumor site, study design, sources of control population, Western *versus* non-Western countries, extensive *versus* nonextensive dietary assessment, type of calcium categorization, and publication bias. Based on these analyses, there was no evidence that these variables modified the relation between calcium intake and risk, with the possible exception of a somewhat stronger RR for proximal *versus* distal colon carcinomas. In light of the degree of heterogeneity among study results and the weak inverse associations, the authors concluded that the results of their analyses did not support the hypothesis that calcium prevents colorectal neoplasia.

The inconclusive findings of analytic epidemiological studies may be partly due to misclassification of calcium intake, because the dietary assessment has usually been at only one point in time. In our study of women (58), data from three dietary questionnaires collected prospectively over 6 years were used to obtain two measures of long-term intake, the average intake and consistent intake (defined as high if women were in the upper tertile on all questionnaires and low if they were in the lower tertile on all questionnaires). To further characterize long-term intake, we conducted analyses excluding women who reported a substantial change in their milk consumption in the 10 years before the baseline questionnaire. The results did not support any major inverse association between calcium intake and risk of colorectal cancer. Although a weak, nonsignificant RR of 0.80 (95% CI, 0.60–1.07) was observed for the association of dietary calcium and colorectal cancer using the baseline dietary questionnaire, we saw no evidence of a dose-response relation (P for trend = 0.25). Data using the three dietary questionnaires did not indicate a clear association for calcium intake. After we excluded women who reported a substantial change in their milk intake, the RR for colorectal cancer for the highest *versus* the lowest categories of dietary calcium was 0.74 (95% CI, 0.36–1.50) for the average intake and 0.70 (95% CI, 0.35–1.39) for the consistent intake. Al-

[2] The abbreviations used are: RR, relative risk; CI, confidence interval.

Table 1 Summary of analytic epidemiologic studies of calcium and colorectal cancer

Author, yr (country, reference no.)	Study type	Study population (no. of cases/no. of controls or population)	RR[a] (95% CI)
Garland, 1985 (United States, 51)	Cohort	49 CR[b]/1954 males	0.32 ($P \leq 0.05$)
Heilbrun, 1985 (United States, 52)	Cohort	100 colon, 59 rectum/8006 Hawaiian-Japanese males	Colon: 0.76 ($P = 0.274$) Rectum: 1.14 ($P = 0.48$)
Wu, 1987 (United States, 53)	Cohort	126 CR/11,888 retirement community	M: 0.86 (0.4–1.7) F: 0.89 (0.5–1.6)
Stemmerman, 1990 (United States, 54)	Cohort	189 colon, 88 rectum/7,195 Hawaiian-Japanese males	Total: 0.77 ($P = 0.16$) Dairy: 0.83 ($P = 0.27$) Nondairy: 0.90 ($P = 0.55$)
Bostick, 1993 (United States, 55)	Cohort	312 colon/35,216 females	Total: 0.68 (0.41–1.11) Dietary: 0.95 (0.57–1.61) Supplemental: 0.66 (0.43–1.02)
Kampman, 1994 (the Netherlands, 56)	Cohort	215 colon, 111 rectum/120,852	Total: 0.92 (0.64–1.24) Nondairy: 1.77 (1.08–2.90) Dairy fermented: 1.14 (0.77–1.68) Dairy unfermented: 0.71 (0.48–1.05)
Kearny, 1996 (United States, 57)	Cohort	203 colon/47,935 males	Total: 0.75 (0.48–1.15) Dietary: 0.81 (0.52–1.28) Dairy: 0.68 (0.42–1.09) Nondairy: 0.86 (0.50–1.48)
Martinez, 1996 (United States, 58)	Cohort	396 colon, 105 rectum/89,448 females	Dietary calcium[c] 1-time: 0.80 (0.60–1.07) Average: 0.74 (0.36–1.50) Consistent: 0.70 (0.35–1.39)
Macquart-Moulin, 1986 (France, 36)	Case-control	399 CR/399 hospital controls	0.71 (NS)[d]
Tuyns, 1987 (Belgium, 38)	Case-control	453 colon, 365 rectum/2,851 population controls	Colon: 1.34 ($P = 0.06$) Rectum: 1.04 ($P = 0.48$)
Kune, 1987 (Australia, 37)	Case-control	715 CR/727 population controls	M: 1.06 (NS) F: 0.56 ($P < 0.01$)
Graham, 1988 (United States, 40)	Case-control	428 colon/428 population controls	NS
Slattery, 1988 (United States, 39)	Case-control	231 colon/391 population controls	M: 0.41 (0.19–0.88) F: 0.50 (0.24–1.06)
Lee, 1989 (China, 41)	Case-control	204 CR/426 hospital controls	Colon: 0.88 (0.53–1.45) Rectum: 0.75 (0.39–1.45)
Negri, 1990 (United States, 42)	Case-control	558 colon, 352 rectum/1,032 hospital controls	Colon: 1.1 (0.8–1.6) Rectum: 1.0 (0.7–1.4)
Fruedenheim, 1990 (United States, 43)	Case-control	422 rectum/422 population controls	M: 1.51 (0.94–2.44) F: 1.63 (0.91–2.91)
Whittemore, 1990 (United States and China, 44)	Case-control	United States 293 colon, 180 rectum/1,192 population controls	United States Colon: 0.89 (0.82–0.95) Rectum: 0.31 (0.16–0.63)
		China 173 colon, 259 rectum/1,296 population controls	China Colon: 0.85 (0.76–0.95)
Benito, 1991 (Spain, 45)	Case-control	286 CR/295 population controls, 203 hospital controls	1.48 (NS)
Peters, 1992 (United States, 46)	Case-control	746 colon/746 population controls	For a 295-mg increase M: 0.86 (0.77–0.96) F: 0.82 (0.70–0.96)
Arbman, 1992 (Sweden, 49)	Case-control	41 CR/41 population controls	Above *versus* below median[e] 0.33 (0.10–0.94)
Zaridze, 1993 (Russia, 47)	Case-control	217 CR/217 population controls	0.52 (0.24–1.13)
Meyer, 1993 (United States, 50)	Case-control	424 colon/414 population controls	1.37 (0.87–1.42)
Ferraroni, 1994 (Italy, 48)	Case-control	828 colon, 498 rectum/2,024 hospital controls	CR: 0.84 (0.65–1.08) Colon: 0.73 (0.54–0.97) Rectum: 1.05 (0.75–1.49)

[a] Relative risk for upper *versus* lower category of intake, unless otherwise noted.
[b] CR, colorectal.
[c] One-time, based on one dietary questionnaire; average, average of three questionnaires during a 6-year period, excluding women who changed their milk intake in the previous 10 years; consistent, high if women were in the upper tertile and low if in lower tertile on three questionnaires during a 6-year period, excluding women who changed their milk intake in the previous 10 years.
[d] NS, not significant.
[e] Reflects 90% CIs; diet history during previous 15 years.

though no significant trends were found, we could not exclude a possible beneficial effect of calcium because of the wide CIs.

It might be argued that the weak or null findings for the association of calcium and colorectal cancer are due to insufficient variation in intake of calcium. However, in our analyses of the average intake, the median dietary calcium values for the lower and upper categories were 445 and 1111 mg/day, respectively. Results of other studies with null or weak inverse associations have also shown similar variations in intake of calcium (42, 48, 55–57).

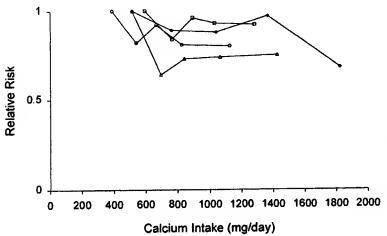

Fig. 2. Prospective studies of calcium and colon/colorectal cancer with 200 cases or more in which a comprehensive assessment of usual diet was used. ◇, Iowa Women's Health Study (55); □, Netherlands Cohort Study (56); △, Health Professionals Follow-Up Study (57); ○, Nurses' Health Study (58). Data points are the median intake for categories of calcium intake. Median for highest and lowest categories of Health Professionals Follow-Up Study and Iowa Women's Health Study was estimated on 0.82 and 1.18 of the quintile cut point, based on the distribution of values in the Nurses' Health Study.

Table 2 Summary of analytic epidemiologic studies of vitamin D and colorectal cancer

Author, yr (country, reference no.)	Study type	Study population (no. of cases/no. of controls or population)	RR[a] (95% CI)
Garland, 1985 (United States, 51)	Cohort	49 CR[b]/1,954 males	0.53 ($P \leq 0.05$)
Heilbrun, 1985 (United States, 52)	Cohort	100 colon, 59 rectum/8,006 Hawaiian-Japanese males	Colon: 1.23 ($P = 0.524$) Rectum: 0.80 ($P = 0.965$)
Bostick, 1993 (United States, 55)	Cohort	312 colon/35,216 females	Total: 0.73 (0.45–1.18) Dietary: 0.98 (0.61–1.58) Supplemental: 0.67 (0.40–1.13)
Kearny, 1996 (United States, 57)	Cohort	203 colon/47,935 males	Total: 0.66 (0.42–1.05) Dietary: 0.88 (0.54–1.42) Supplemental: 0.48 (0.22–1.02) Dairy: 0.75 (0.47–1.22) Nondairy: 0.66 (0.42–1.04)
Martinez, 1996 (United States, 58)	Cohort	396 colon, 105 rectum/89,448 females	Dietary vitamin D[c] 1-time: 0.84 (0.63–1.13) Average: 0.72 (0.34–1.54) Consistent: 0.59 (0.30–1.16) Total vitamin D 1-time: 0.88 (0.66–1.16) Average: 0.42 (0.19–0.91) Consistent: 0.33 (0.16–0.70)
Benito, 1991 (Spain, 45)	Case-control	286 CR/295 population controls, 203 hospital controls	0.74 (NS)[d]
Peters, 1992 (United States, 46)	Case-control	746 colon/746 population controls	For a 108-IU increase: M: 1.10 (0.95–1.26) F: 1.08 (0.90–1.28)
Ferraroni, 1994 (Italy, 48)	Case-control	828 colon, 498 rectum/2,024 hospital controls	CR: 0.74 (0.58–0.95) Colon: 0.75 (0.56–1.01) Rectum: 0.73 (0.51–1.03)

[a] Relative risk for upper *versus* lower category of intake, unless otherwise noted.
[b] CR, colorectal.
[c] One-time, based on one dietary questionnaire; average, average of three questionnaires during a 6-year period, excluding women who changed their milk intake in the previous 10 years; consistent, high if women were in the upper tertile and low if in the lower tertile on three questionnaires during a 6-year period, excluding women who changed their milk intake in the previous 10 years.
[d] NS, not significant.

To address the possibility that an effect of calcium intake exists at the early stages of carcinogenesis, the role of this nutrient could be assessed in the development of the precursor lesion for colorectal cancer, the adenomatous polyp. Few case-control studies (64–67) and one prospective study of the Nurses' Health Study and the Health Professionals Follow-Up Study (68) have been reported in the literature. Nonsignificant inconsistent findings were reported in the case-control studies, and weak positive associations were reported in the prospective study. Thus, results of studies of adenomatous polyps do not support an effect of calcium in the early colon carcinogenesis sequence. This conclusion is also supported by the results of the recent meta-analysis (63), in which the summary RR using adenomas as end points from four studies was 1.13 (95% CI, 0.91–1.39).

Vitamin D. Epidemiolgic data on vitamin D and colorectal cancer are sparse (Table 2). Four (51, 55, 57, 58) of the five

prospective studies have reported inverse associations for dietary vitamin D and colon or colorectal cancer, but this was only significant in the Western Electric study (51). In the Iowa Women's Health Study (55) and the Health Professionals Follow-Up Study (57), a significant inverse age-adjusted RR was observed for total vitamin D and risk of colon cancer, although this was attenuated and was no longer significant after multivariate adjustment. Of the three published case-control studies of vitamin D and colon or colorectal cancer, two (45, 46) show inconsistent, nonsignificant findings, and one (48) reported a significant inverse association. It is interesting to note that stronger associations were seen when supplemental or total (dietary plus supplemental) vitamin D intake was considered.

The results of our study (58) for vitamin D are somewhat suggestive of an inverse association with colorectal cancer. Overall, stronger inverse associations were seen for vitamin D than for calcium. In the analyses excluding women who reported a substantial change in their milk consumption 10 years in the past, the strongest RRs for colorectal cancer were observed for women who remained in the upper tertile of total vitamin D intake on all three questionnaires as compared with those who were in the lower tertile (RR, 0.33; 95% CI, 0.16–0.70). Similarly, a significant inverse association was observed for women in the upper *versus* the lower category of average intake of total vitamin D (RR, 0.42; 95% CI, 0.19–0.91). These results are consistent with published studies in which stronger associations were observed when supplemental sources of vitamin D were considered (55, 57). Because the protective effect seems to be stronger for total vitamin D, the possibility that something other than vitamin D in multivitamin supplements contributes to this apparent effect cannot be ruled out.

In summary, results of published epidemiological studies suggest that higher calcium intakes are not associated with a substantially lower risk of colorectal cancer; however, the possibility that calcium intake has a weak or modest effect on the occurrence of colorectal cancer cannot be excluded. The findings for vitamin D are suggestive of an inverse association, particularly for total vitamin D in relation to colorectal cancer. Additional investigations, in particular, prospective studies with extended follow-up and repeated measures of diet, are needed to more fully resolve these issues. Because the latency for aspirin use and diagnosis of colon cancer seems to be at least a decade (69) and that for cigarette smoking seems to be even longer (70–71), studies of diet and colorectal cancer will need to continue for at least several decades before an effect can be excluded with confidence. Further insight may be added by ongoing randomized trials. In the Women's Health Initiative, women are randomized to a combination of calcium and vitamin D or placebo (72). Because these two agents are completely confounded, any observed effect could not be attributed to one or the other. Furthermore, lack of effect could readily be attributed to insufficient duration of intervention. At least one randomized trial of calcium supplementation and recurrence of colon adenoma will soon be completed. If the epidemiological data were more clear in showing an inverse association, a significant reduction in polyp recurrence would strongly support a causal interpretation. However, because the epidemiological data are not clear and polyp recurrence is a surrogate end point, a positive result from the recurrence study would reinforce the need for longer-term prospective studies with colorectal cancer as the end point. At this time, there does not seem to be justification for additional intervention trials of calcium supplementation.

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